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L8: Entry 18 of 33 File: USPT Mar 13, 2001

DOCUMENT-IDENTIFIER: US 6200985 B1
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TITLE: Rapamycin derivatives

Abstract Text (1):
Rapamycin derivatives are disclosed of the formula: ##STR1##

Brief Summary Text (1):
The present invention relates to rapamycin derivatives, a process for their production, their use as a pharmaceutical and pharmaceutical compositions containing them.

Brief Summary Text (2):
Rapamycin is a known macrolide antibiotic produced by Streptomyces hygroscopicus, having the structure depicted in Formula A: ##STR2##

Brief Summary Text (3):
See, e.g., McAlpine, J. B., et al., J. Antibiotics (1991) 44: 688; Schreiber, S. L., et al., J. Am. Chem. Soc. (1991) 113: 7433; U.S. Pat. No. 3,929,992. (There have been various numbering schemes proposed for rapamycin. To avoid confusion, when specific rapamycin derivatives are named herein, the names are given with reference to rapamycin using the numbering scheme of formula A.) Rapamycin is a potent immunosuppressant and has also been shown to have antitumor and antifungal activity. Its utility as a pharmaceutical, however, is restricted by its very low and variable bioavailability. Moreover, rapamycin is insoluble and lacks stability, making it difficult to formulate stable galenic compositions.

Brief Summary Text (4):
Numerous derivatives of rapamycin are known. Certain 40-O-substituted rapamycins are described in, e.g., in U.S. Pat. No. 5,258,389 and WO 94/09010 (O-alkyl rapamycins); WO 92/05179 (carboxylic acid esters), U.S. Pat. No. 5,118,677 (amide esters), U.S. Pat. No. 5,118,678 (carbamates), U.S. Pat. No. 5,100,883 (fluorinated esters), U.S. Pat. No. 5,151,413 (acetals), and U.S. Pat. No. 5,120,842 (silyl ethers).

Brief Summary Text (5):
It has now surprisingly been discovered that certain novel derivatives of rapamycin have an improved pharmacologic profile over rapamycin, and exhibit greater stability.

Brief Summary Text (38):
(i) 32-deoxo-rapamycin;

Brief Summary Text (39):
(ii) 16-O-pent-2-ynyl-32deoxo-rapamycin;

Brief Summary Text (40):
(iii) 16-O-pent-2-ynyl-32-deoxo40-O-(2-hydroxy-ethyl)rapamycin

Brief Summary Text (41):
(iv) 16-O-pent-2-ynyl-32(S)-dihydro-rapamycin;

Brief Summary Text (42):
(v) 16-O-pent-2-ynyl-32(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin;

Brief Summary Text (43):
(vi) 32(S)-dihydro-40-O-(2-methoxyethyl-rapamycin;

Brief Summary Text (44):
(vii) 32(S)-dihydro-40O-(2-hydroxyethyl)rapamycin.

Detailed Description Text (3):
To a stirred, cooled (-78.degree.) solution of 26.1 g (22.85 mmol) of 28,40-bis--O-TES-rapamycin in 260 ml of TBF is added 50.3 ml (50.3 mmol) of a 1M solution of lithium-tri-t.-butoxyaluminum hydride in TBF. The resulting mixture is allowed to warm to -15.degree. over 2 hours. Then the cooling bath is replaced by an ice bath, bringing the temperature to 0.degree., and stirring is continued for 1 hour at this temperature. The reaction mixture is poured into a separating funnel containing 750 ml of ethyl acetate and 400 ml of ice-cold 2N aqueous citric acid and briefly shaken. The aqueous layer is separated and extracted twice with cold ethyl acetate. The combined organic solution is washed with ice-cold 2N aqueous citric acid, water, saturated aqueous sodium bicarbonate and twice with saturated brine, then dried over anhydrous sodium carbonate, filtered and concentrated under reduced pressure. The residue, consisting of a mixture of 32(R)-dihydro-28,40-bis-O-TES-rapamycin and (32R) 9,32-bis-dihydro-28,40-bis-O-TES-rapamycin, is dissolved without further purification in 260 ml of methanol. This solution is cooled to 0.degree. and treated with 6.85 g (34.31 mmol) of cupric acetate. After stirring for I hour, the resulting suspension is diluted with methyl-t.-butyl ether and washed twice with water and twice with saturated brine. The aqueous layers are backextracted with methyl-t-butyl ether. The combined organic solution is dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by silica gel chromatography (60:40 hexane/methyl-t-butyl ether) to afford pure 32(R)-dihydro-28,40-bis-O-TES-rapamycin as a white solid.

Detailed Description Text (6):
To a stirred, cooled (-15.degree.) solution of 20.69 g (18.10 mmol) of 32(R)-dihydro-28,40-bis-O-TES-rapamycin and 7.55 ml (54.27 mmol) of triethylamine in 200 ml of methylene chloride is added 2.10 ml (27.02 mmol) of methanesulfonyl chloride. The mixture is stirred for 20 minutes, then diluted with ethyl acetate and saturated aqueous sodium bicarbonate is added. The layers are separated and the aqueous layer is extracted three times with ethyl acetate. The combined organic phase is washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue may be purified by column chromatography on silica gel (80:20 hexane/ethyl acetate) affording pure 32(R)-dihydro-32-O-mesyl-28,40-bis-O-TES-rapamycin as a white solid, but routinely the crude product is used in the subsequent step without further purification.

Detailed Description Text (9):
A mixture of 22.35 g (18.30 mmol) of 32(R)-dihydro-32-O-mesyl-28,40-bis-O-TES-rapamycin, 27.50 g (183.33 mmol) of sodium iodide and 6.3 ml (36.68 mmol) of diisopropylethylamine in 400 ml of TBF is heated to reflux for 6 hours, then is allowed to cool to room temperature. The resulting mixture is diluted with ethyl acetate and treated with 38.4% aqueous sodium bisulfite. The layers are separated. The organic phase is washed three times with saturated aqueous sodium bicarbonate and once with saturated brine, then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel (83:17 hexane/ethyl acetate) to afford pure 32(S)-deoxo-32-iodo-28,40bis-0-TES-rapamycin.

Detailed Description Text (12):
To a stirred, cooled (0.degree.) solution of 16.79 g (13.19 mmol) of 32(S)-deoxo-32-iodo-28,40-bis-O-TES-rapamycin in 190 ml of toluene is added 7 ml (26.38 mmol) of tributyltin hydride followed by 1.3 ml (1.30 mmol) of a 1M solution of triethylborane in hexane. This mixture is stirred for 30 minutes and quenched with saturated aqueous ammonium chloride. The layers are separated and the aqueous layer is extracted twice with ethyl acetate. The combined organic layers are washed with water, saturated aqueous sodium bicarbonate, water and three times with saturated brine, then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel (75:25

hexane/methyl-t-butyl ether) to afford pure 32-deoxo-28,40-bis-O-TES-rapamycin as a white solid.

Detailed Description Text (15):
To a stirred, cooled (-15.degree.) solution of 10.73 g (9.52 mmol) of 32-deoxo-28,40-bis-O-TES-rapamycin in 85 ml of methanol is added dropwise 9.5 ml of 2N aqueous sulfuric acid. After the addition is complete, the reaction mixture is warmed to 0.degree. and stirred for 1.5 hour, then diluted with ethyl acetate and quenched with saturated sodium bicarbonate. The layers are separated and the aqueous layer is extracted with three portions of ethyl acetate. The combined organic phase is washed three times with saturated sodium bicarbonate and with brine, then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is dissolved in-diethyl ether whereupon the desired 32-deoxo-rapamycin crystallizes (colorless crystals).

Detailed Description Text (19):
16-pent-2-ynyloxy-32(S)-dihydro rapamycin (R.sub.1 =pent-2-ynyl; R.sub.2 =II wherein R.sub.3 =H and R.sub.4 =CH.sub.3 ; X=OH; Y=O)

Detailed Description Text (24):
16-pent-2-ynyloxy-32(S)-dihydro rapamycin (Alternative Route)

Detailed Description Text (25):
Rapamycin is reacted with 2-pentyn-1-ol in a procedure analogous to that of Example 2 to yield 16-pent-2-ynyloxy-rapamycin.

Detailed Description Text (26):
To a stirred, cooled (-77.degree.) solution of 175 g (18.1 mmol) of 16demethoxy-16-pent-2-ynyloxy-rapamycin in 180 ml of TBF are added 21.7 ml (21.7 mmol) of a 1M solution of sodium triethylborohydride in TBF. After 1 h at -77.degree. the reaction is quenched and neutralized with a 10% citric acid aqueous solution. The reaction mixture is then allowed to come to room temperature and most of the THF is removed by evaporation under reduced pressure. The resulting solution is extracted twice with ethyl acetate, the organic phases are combined and dried over sodium sulfate. After evaporation of the solvent the crude reaction product is chromatographed over silica gel eluting with hexane/acetone 7/3. The final purification is achieved by preparative HPLC (RP-18, 76:24 methanol:water) to afford the title compound as a white amorphous solid.

Detailed Description Text (29):
32(S)dihydro-400-(2-methoxy)ethyl-rapamycin (R.sub.1 =CH.sub.3 ; R.sub.2 =II wherein R.sub.3 =2-methoxyethyl and R.sub.4 =CH.sub.3 ; X=OH; Y=0)

Detailed Description Text (30):
To a stirred, cooled (0.degree.) solution of 2.17 g (2.00 mmol) of 40-O-(2-methoxy)ethyl-28-O-TES-rapamycin in 20 ml of THF is added dropwise 4.4 ml (4.4 mmol) of a 1M solution of L-Selectride.RTM. in THF. The resulting yellow solution is stirred for three hours at 0.degree. and the excess hydride reagent is quenched by the addition of 2 ml of MeOH. The solution is diluted with methyl-t-butyl ether and saturated aqueous Rochelle's salt solution is added. This mixture is allowed to warm to room temperature and stirring is continued for 15 minutes. The layers are separated and the organic solution is washed with cold 1N HCl, saturated brine, 1N sodium bicarbonate and again with brine. The aqueous washings are back-extracted with methyl-t-butyl ether. The combined organic layers are dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford a crude mixture of the 32S and 32R isomers of 32-dihydro-40-(2-methoxy)ethyl-28-O-TES-rapamycin.

Detailed Description Text (31):
The crude product obtained above is dissolved in 20 ml of acetonitrile and cooled to 00. To the resulting solution is added 2 ml of HF pyridine complex. Stirring is continued for 1 hour and 1N sodium bicarbonate is added. This mixture is extracted three times with metyl-t-butyl ether. The combined organic solution is washed with 1N sodium bicarbonate and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification is carried out by reverse phase HPLC (RP 18, 5 .mu.m, 50:50-100:0 acetonitrile-water over 60 minutes) affording

32(S)-dihydro40-O-(2-methoxy)ethyl rapamycin and
32(R)-dihydro-40-O-(2-methoxy)ethyl-rapamycin as by-product.

Detailed Description Text (32):
32(S)-dihydro40-O-(2-methoxy)ethyl-rapamycin: .sup.1 H NMR (CDCl.sub.3) 2:1 mixture of rotamers, chemical shifts in parentheses refer to the minor rotamer .delta. 0.77 (1H, dd, H-38 ax), 1.67 (6H, s, C17-CH.sub.3 and C29-CH.sub.3), 2.50 (1H, m, H-31), 3.01 (1H, m, H-25), 3.12 (2H, m, H-39 and H.sub.40), 3.14 (3.15) (3H, s, OCH.sub.3), 3.28 (1H, m, H-32), 3.36 (3.34) (3H, s, OCH.sub.3), 3.39 (3.38) (3H, s, OCH.sub.3), 3.48 (3.46) (3H, s, OCH.sub.3), 3.55 and 3.75 (4H, 2m, OCH.sub.2 CH.sub.2 O), 3.84 (1H, n, H-14), 4.12 (4.16) (1H, d, H-28), 4.73 (1H, s, C10-OH), 5.03 (1H, m, H-34)

Detailed Description Text (35):
(32S)-dihydro40-(2-hydroxy)ethyl-rapamycin (R=CH.sub.3 ; R.sub.2 =II wherein R.sub.3 =--CH.sub.2 CH.sub.2 OH and R.sub.4 =CH.sub.3 ; X=OH; Y=O)

Detailed Description Text (37):
(32S)dihydro40-O-(2-hydroxy)ethyl-rapamycin: .sup.1 H NMR (CDCl.sub.3) 1.7:1 mixture of rotamers, chemical shifts in parentheses refer to the minor rotamer .delta. 0.76 (1H, dd, H-38ax), 2.50 (1H, m, H-31), 3.10 (1H, m, H-39), 3.13 (3.14) (3H, s, C16-OCH.sub.3), 3.20 (1H, m, H-40), 3.28 (1H, m, H-32), 3.36 (3.38) (3H, s, C27-OCH.sub.3), 3A5 (3A3) (3.41) (3H, s, C39-OCH.sub.3), 3.50 (1H, d, H-27), 3.58 and 3.70 (4H, m, OCH.sub.2 CH.sub.2 OH), 4.12 (4.16) (1H, d, H-28), 5.06 (1H, m, H-34), 5.60 (1H, dd, H-22), 5.99 (1H, d, H-18), 6.17 (1H, dd, H-21), 6.33 (1H, dd, H-20), 6.42 (1H, dd, H-19)

Detailed Description Text (40):
16-pent-2-ynyloxy-32-deoxo rapamycin (R.sub.1 =pent-2-ynyl; R.sub.2 =II wherein R.sub.3 =H and R.sub.4 =CH.sub.3 ; X=H; Y=O)

Detailed Description Text (47):
The Mixed Lymphocyte Reaction was originally developed in connection with allografts, to assess the tissue compatibility between potential organ donors and recipients, and is one of the best established models of immune reaction in vitro. A murine model MLR, e.g., as described by T. Meo in "Immunological Methods", L. Lefkovits and B. Pernis, Eds., Academic Press, N.Y. pp. 227-239 (1979), is used to demonstrate the immunosuppressive effect of the Compounds of formula I. Spleen cells (2.times.10.sup.5 /well) from Balb/c mice (female, 8-10 weeks) are co-incubated on microtiter plates for 5 days with 0.5.times.10.sup.6 irradiated (2000 rads) or mitomycin C treated spleen cells from CBA mice (female, 8-10 weeks). The irradiated allogeneic cells induce a proliferative response in the Balb/c spleen cells which can be measured by labeled precursor incorporation into the DNA. Since the stimulator cells are irradiated (or mitomycin C treated) they do not respond to the Balb/c cells with proliferation but do retain their antigenicity. The antiproliferative effect of the Compounds of formula I on the Balb/c cells is measured at various dilutions and the concentration resulting in 50% inhibition of cell proliferation (IC.sub.50) is calculated. The inhibitory capacity of the test sample may be compared to rapamycin and expressed as a relative IC.sub.50 (i.e. IC.sub.50 test sample/IC.sub.50 rapamycin). The compounds of Examples 1 and 2 have been found to have in this test a relative IC.sub.50 of 0.3 and 0.08, respectively.

Detailed Description Text (49):
The capacity of the Compounds of formula I to interfere with growth factor, associated signalling pathways is assessed using an interleukin-6 (IL-6)-dependent mouse hybridoma cell line. The assay is performed in 96-well microtiter plates. 5000 cells/well are cultivated in serum-free medium (as described by M. H. Schreier and R. Tees in Immunological Methods, I. Lefkovits and B. Pernis, Eds., Academic Press 1981, Vol. 1, pp. 263-275), supplemented with 1 ng recombinant IL-6/ml. Following a 66 hour incubation in the absence or presence of a test sample, cells are pulsed with 1 .mu.Ci (3-H)thymidine/well for another 6 hours, harvested and counted by liquid scintillation. (3-H)thymidine incorporation into DNA correlates with the increase in cell number and is thus a measure of cell proliferation. A dilution series of the test sample allows the calculation of the concentration resulting in 50% inhibition of cell proliferation (IC.sub.50). The inhibitory capacity of the test sample may be compared to rapamycin and expressed as a relative IC.sub.50 (i.e. test sample/IC.sub.50

rapamycin). The compounds of Examples 1 and 2 have been found to have in this test a relative IC.sub.50 of 0.2 and 0.09, respectively.

Detailed Description Text (51):
Rapamycin and the structurally related immunosuppressant, FK-506, are both known to bind in vivo to macrophilin-12 (also known as FK-506 binding protein or FKBP-12), and this binding is thought to be related to the immunosuppressive activity of these compounds. The Compounds of formula I also bind strongly to macrophilin-12, as is demonstrated in a competitive binding assay. In this assay, FK-506 coupled to BSA is used to coat microtiter wells. Biotinylated recombinant human macrophilin-12 (biot-MAP) is allowed to bind in the presence or absence of a test sample to the immobilized FK-506. After washing (to remove non-specifically bound macrophilin), bound biot-MAP is assessed by incubation with a streptavidin-alkaline phosphatase conjugate, followed by washing and subsequent addition of p-nitrophenyl phosphate as a substrate. The read-out is the OD at 405 nm. Binding of a test sample to biot-MAP results in a decrease in the amount of biot-MAP bound to the FK-506 and thus in a decrease in the OD405. A dilution series of the test sample allows determination of the concentration resulting in 50% inhibition of the biot-MAP binding to the immobilized FK-506 (IC.sub.50). The inhibitory capacity of a test sample is compared to the IC.sub.50 of free FK506 as a standard and expressed as a relative IC.sub.50 (i.e., IC.sub.50 test sample/IC.sub.50 -free FK506). In this assay, the compounds of Examples 1, 2 and 5 have been found to have a relative IC.sub.50 of 1, 2.8 and 25, respectively.

Detailed Description Text (91):
The compounds of formula I are administered by any conventional route, in particular enterally, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Suitable unit dosage forms for oral administration comprise, e.g. from 1 to 50 mg of a compound of formula I, usually 1 to 10 mg. Pharmaceutical compositions comprising the compounds of formula I may be manufactured in conventional manner, e.g. analogously to pharmaceutical compositions comprising rapamycin, e.g., as described in EPA 0 041 795.

Detailed Description Text (102):
D. a kit or package for use in immunosuppression, inflammation or infections as indicated above, including a pharmaceutical composition comprising a compound of formula I and a pharmaceutical composition comprising either an immunosuppressant or immunomodulatory drug or an anti-inflammatory agent or an anti-infective agent.

CLAIMS:

4. A method of claim 1, wherein the compound is 16-pent-2-ynyloxy-32(S)-dihydro-rapamycin or 16-pent-2-ynyloxy-32(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin.

5. A method of claim 1, wherein the compound is 32-deoxo-rapamycin or 16-pent-2-ynyloxy-32-deoxo-rapamycin.

6. A method of claim 1 for preventing acute or chronic organ or tissue transplant rejection, wherein the compound is 16-pent-2-ynyloxy-32(S)-dihydro-rapamycin or 16-pent-2-ynyloxy-32(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin.

7. A method of claim 1 for preventing acute or chronic organ or tissue transplant rejection, wherein the compound is 32-deoxo-rapamycin or 16-pent-2-ynyloxy-32-deoxo-rapamycin.

8. A method of claim 1 for treating acute or chronic organ or tissue transplant rejection, wherein the compound is 16-pent-2-ynyloxy-32(S)-dihydro-rapamycin or 16-pent-2-ynyloxy-32(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin.

9. A method of claim 1 for treating acute or chronic organ or tissue transplant rejection, wherein the compound is 32-deoxo-rapamycin or 16-pent-2-ynyloxy-32-deoxo-rapamycin.

10. A method of claim 1 for preventing transplant vasculopathies, wherein the compound is 16-pent-2-ynyloxy-32(S)-dihydrorapamycin or 16-pent-2-ynyloxy-32(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin.

11. A method of claim 1 for preventing transplant vasculopathies, wherein the compound is 32-deoxo-rapamycin or 16-pent-2-ynyloxy-32-deoxo-rapamycin.

12. A method of claim 1 for treating transplant vasculopathies, wherein the compound is 16-pent-2-ynyloxy-32(S)-dihydro-rapamycin or 16-pent-2-ynyloxy-32(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin.

13. A method of claim 1 for treating transplant vasculopathies, wherein the compound is 32-deoxo-rapamycin or 16-pent-2-ynyloxy-32-deoxo-rapamycin.

17. A method of claim 14, wherein the compound is 16-pent-2-ynyloxy-32(S)-dihydro-rapamycin or 16-pent-2-ynyloxy-32(S)dihydro -40-O-(2-hydroxyethyl)-rapamycin.

18. A method of claim 14, wherein the compound is 32-deoxo-rapamycin or 16-pent-2-ynyloxy-32-deoxo-rapamycin.

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L8: Entry 20 of 33 File: USPT Aug 29, 2000

DOCUMENT-IDENTIFIER: US 6110910 A
TITLE: Carbocyclic heterocyclic fused-ring quinolinecarboxylic acids useful as immunosuppressive agents

Brief Summary Text (22):
Presently, cyclosporin A, an immunosuppressive agent, used in combination with other adjunctive therapies, such as azathioprine and corticosteroids, is the treatment of choice for the prevention of organ transplantation rejection. Other immunosuppressive agents such as azathioprine, corticosteroids (such as prednisone), OKT3, FK506, mycophenolic acid or the 2-(N-morpholino)ethyl ester thereof, 15-deoxyspergualin, rapamycin, mizoribine, misoprostol and anti-interleukin-2 receptor antibodies, have been used or have been suggested to be useful in the treatment and/or prevention of organ transplantation rejection.

Brief Summary Text (25):
The carbocyclic and heterocyclic fused-ring quinolinecarboxylic acid compounds of this invention can be used alone or in combination with one or more additional known immunosuppressive agents, such as cyclosporin A (CSA or CsA) and analogs thereof, FK506 (or FK-506) and analogs thereof, corticosteroids, azathioprine (AZA), mycophenolic acid or the 2-(N-morpholino)ethyl ester thereof, mycophenolate mofetil, rapamycin, 15-deoxyspergualin, mizoribine, leflunomide, OKT3, anti-interleukin-2 receptor antibodies, misoprostol, methotrexate, cyclophosphamide, and anti-lymphocyte/thymocyte serums, thereby to reduce the dosage required and associated adverse effects of these immunosuppressive agents.

Brief Summary Text (32):
additional immunosuppressive agent. Such additional immunosuppressive agent may be selected from the group including but not limited to cyclosporin A (CSA or CsA) and analogs thereof, FK506 and analogs thereof, corticosteroids, azathioprine (AZA), mycophenolic acid or the 2-(N-morpholino)ethyl ester thereof, mycophenolate mofetil, rapamycin, 15-deoxyspergualin, mizoribine, leflunomide, OKT3, antiinterleukin-2 receptor antibodies, misoprostol, methotrexate, cyclophosphamide, and antilymphocyte/thymocyte serums.

Brief Summary Text (88):
The present invention also provides methods of treatment and/or prevention of immunological disorders including organ transplantation rejection, graft versus host disease, psoriasis, autoimmune diseases, and chronic inflammatory diseases in a mammal comprising administering to the mammal in a therapeutically effective amount for the treatment of a desired aforesaid disease a combination of: (i) a compound of Formulas 1-4 as described below and (ii) at least one additional immunosuppressive agent. Such additional immunosuppressive agent may be selected from the group including but not limited to cyclosporin A (CSA or CsA) and analogs thereof, FK506 and analogs thereof, corticosteroids, azathioprine (AZA), mycophenolic acid or the 2-(N-morpholino)ethyl ester thereof, mycophenolate mofetil, rapamycin, 15-deoxyspergualin, mizoribine, leflunomide, OKT3, anti-interleukin-2 receptor antibodies, misoprostol, methotrexate, cyclophosphamide, and anti-lymphocyte/thymocyte serums.

Brief Summary Text (104):
Rapamycin is described in U.S. Pat. Nos. 4,650,803; 4,316,885; 4,885,171; 3,993,749 and 3,929,992, all assigned to Ayerst.

Brief Summary Text (110):

This invention also includes pharmaceutical kits comprising or consisting essentially of: a pharmaceutical composition comprising a compound of Formulas 1-4; or a compound of Formulas 1-4 together with a pharmaceutical composition comprising at least one additional immunosuppressive agent. This invention also provides methods of using such pharmaceutical kits for the treatment of organ transplantation rejection, graft versus host disease, psoriasis and autoimmune diseases, including but not limited to rheumatoid arthritis, systemic lupus erythematous, multiple sclerosis, myasthenia gravis, insulin dependent diabetes, as well as chronic inflammatory disease including but not limited to Crohn's disease and primary biliary cirrhosis, in a mammal.

Brief Summary Text (111):
This invention also includes combination products comprising pharmaceutical compositions comprising a compound of Formulas 1-4 in physical combination or in a single dosage form with a second immunosuppressive agent, to pharmaceutical kits containing these combination products, and to methods of using these combination products for the treatment of organ transplantation rejection, graft versus host disease, psoriasis and autoimmune diseases, including but not limited to rheumatoid arthritis, systemic lupus erythematous, multiple sclerosis, insulin dependent diabetes, myasthenia gravis, as well as chronic inflammatory disease including but not limited to Crohn's disease and primary biliary cirrhosis, in a mammal.

Detailed Description Text (121):
Such second immunosuppressive agent (component (ii)) may be selected from the group consisting of, but not limited to: cyclosporin A, azathioprine, corticosteroids such as prednisone, OKT3, FK506, mycophenolic acid or the 2-(N-morpholino)ethyl ester thereof, 15-deoxyspergualin, rapamycin, mizoribine, misoprostol and anti-interleukin-2 (IL-2) receptor antibodies. The combination treatment can be administered to treat immuno-modulatory disorders and inflammatory diseases and particularly to prevent or treat organ transplantation rejection, graft versus host disease, psoriasis, rheumatoid arthritis, autoimmune diseases, and chronic inflammatory diseases, and related disorders, by any means that produces contact of the active ingredient(s) with the agent's site of action in the body of a mammal.

CLAIMS:

11. The method of claim 10 wherein the additional immunosuppressive agent (ii) is selected from the group consisting of cyclosporin A, azathioprine, a corticosteriod, OKT3, FK506, mycophenolic acid or the 2-(N-morpholino)ethyl ester thereof, mycopheolate mofetil, 15-dioxyspergualin, rapamycin, mizoribine, leflunomide, misoprostol, methotrexate, cyclophosphamide, anti-lymphocyte/thymocyte serums or an anti-interleukin-2 receptor antibody.

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L14: Entry 37 of 41 File: USPT Oct 31, 2000

DOCUMENT-IDENTIFIER: US 6139847 A
**** See image for Certificate of Correction ****
TITLE: Combined use of angiotensin inhibitors and nitric oxide stimulators to treat fibrosis

Brief Summary Text (11):
Likewise, a number of agents which affect smooth muscle cell proliferation have been tested. These compositions have included heparin, coumarin, aspirin, fish oils, calcium antagonists, steroids, prostacyclin, rapamycin, dipyridamole, ultraviolet irradiation, gamma (.gamma.)-interferon, serotonin inhibitors, methotrexate and mycophenolic acid, either alone or in various combinations.

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L14: Entry 39 of 41 File: USPT May 26, 1998

DOCUMENT-IDENTIFIER: US 5756673 A
TITLE: Regulation of smooth muscle cell proliferation

Brief Summary Text (14):
A number of agents which affect cell proliferation have been tested as pharmacological treatments for stenosis and restenosis in an attempt to slow or inhibit proliferation of SMCs. These compositions have included heparin, coumarin, aspirin, fish oils, calcium antagonists, steroids, prostacyclin, rapamycin, dipryidamole, ultraviolet irradiation, gamma (.gamma.)-interferon, serotonin inhibitors, methotextrate and mycophenolic acid, either alone or in various combinations. For example, heparin is commonly used following coronary angioplasty to reduce the incidence of acute thrombotic occlusion and reduce the proliferation of SMCs (Guyton et al., Circ. Res. 46:625, 1980). These activities were demonstrated in vitro and confirmed in vivo in experiments on rat arterial SMC proliferation after balloon catheter injury (Gordon et al., Circulation 76:213, 1987). Wai et al. determined that a hybrid protein consisting of the ribosome inhibitor, saponin, fused to basic fibroblast growth factor (FGF), killed proliferating FGF-receptor expressing SMCs, but not quiescent receptor negative cells (Wai et al., Circulation 82:208, 1990). This same hybrid protein also inhibited intimal thickening following vascular injury.

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	DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ		
L14	(rapamycin or CD40L or gp39 or CD40 adj ligand) same (fish adj oil or 'omega-3')	41	L14
L13	(rapamycin or CD40L or gp39 or CD40 adj ligand) and (fish adj oil or 'omega-3')	94	L13
L12	L10 and (fish adj oil or 'omega-3')	0	L12
L11	L10 and (fish adj oil or omega)	1	L11
L10	rapamycin same (CD40L or gp39 or CD40 adj ligand)	73	L10
L9	rapamycin and (CD40L or gp39 or CD40 adj ligand)	366	L9
L8	rapamycin and (kit or kits)same (immunosuppressi$)	33	L8
L7	L1 and (kit or kits)same (immunosuppressi$)	2	L7
L6	L1 and (kit or kits)	20	L6
L5	L4	2	L5
L4	L2 and kit	2	L4
L3	L2 and rapamycin	3	L3
L2	L1 and (CD40L or gp39 or CD40 adj ligand)	5	L2
L1	strom.in.	971	L1

END OF SEARCH HISTORY

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L13: Entry 44 of 94 File: PGPB Jul 25, 2002

DOCUMENT-IDENTIFIER: US 20020099067 A1
TITLE: Pharmaceutical compositions for sparingly soluble therapeutic agents

Summary of Invention Paragraph (17):
[0017] Particularly suitable sparingly soluble therapeutic agents are immunosuppressants having a macrolide structure, typically cyclosporin A, cyclosporin G, rapamycin, tacrolimus, deoxyspergualin, mycophenolate-mofetil, gusperimus, non-steroidal antiphlogistic agents, typically acetylsalicylic acid, ibuprofen or S(+)-ibuprofen, indomethacin, diclofenac, piroxicam, meloxicam, tenoxicam, naproxen, ketoprofen, flurbiprofen, fenoprofen, felbinac, sulindac, etodolac, oxyphenbutazone, phenylbutazone, nabumetone; dihydro-pyridine derivatives having cardiovascular activity, e.g. nifedipine, nitrendipine, nimodipine, nisoldipine, isradipine, felodipine, amlodipine, nilvadipine, lacidipine, benidipine, masnidipine, furnidipine, niguldipine; depressants and stimulants, typically .alpha.-liponic acid, muramyl peptides, e.g. muramyl dipeptide or muramyl tripeptide, romurtid, fat-soluble vitamins, typically vitamin A, D, E or F; alkaloids, e.g. vincopectin, vincristine, vinblastin, reserpine, codeine, ergot alkaloids, typically bromocriptine, dihydroergotamine, dihydroergocristine; antitumour agents, e.g. chlorambucil, etoposide, teniposide, idoxifen, tallimustin, teloxantron, tirapazamine, carzelesin, dexniguldipine, intoplicin, idarubicin, miltefosin, trofosfamide, teloxantrone, melphalan, lomustine, 4,5-bis(4'fluoroanilino)phthalimide; 4,5-dianilinophthalimide; immunomodulators, typically thymoctonan, prezatid copper acetate; antiinfectives, e.g. erythromycin, daunorubicin, gramicidin, doxorubicin, amphotericin B, gentamycin, leucomycin, streptomycin, ganefromycin, rifamexil, ramoplanin, spiramycin; antimycotic agents, typically fluconazole, ketoconazole, itraconazole; H2-receptor antagonists, typically famotidine, cimetidine, ranitidine, roxatidine, nizatidine, omeprazole, proteinkinase inhibitors, e.g.
N-[4-methyl-3-(4-pyridin-3-ylpyrimidin-2-ylamino)phenyl]benzamide,
N-benzoyl-staurosporin; HIV-1-protease inhibitors, e.g.
BOC-Phe.sup.cPhe-Val-Phe-morpholine or its O-[2-(2-methoxyethoxy)acetoxy] derivative; leucotriene antagonists, typically N-[4-(5-cyclopentyloxycarb-onylamino-1-methylindol-3-ylmethyl)-3-methoxybenzoyl]-2-vinyloxy]benzenesu- lfonamide.

Summary of Invention Paragraph (18):
[0018] Particularly preferred therapeutic agents are cyclosporins, rapamycin, tacrolimus, deoxyspergualin, mycophenolate-mofetil, nifedipine, nimodipine, etoposide, ibuprofen and .alpha.-liponic acid.

Summary of Invention Paragraph (39):
[0039] Suitable triglycerides of natural orgin are, for example, ground nut oil, sesame oil, sunflower oil, olive oil, corn oil, soybean oil, castor oil, cottonseed oil, rape-seed oil, thistle oil, grape-seed oil, fish oil or neutral oil.

Detail Description Table CWU (6):
6 Composition for filling into soft gelatin capsules; amounts in mg per filled capsule, size of soft gelatin capsules: 6 minims, oblong. 1 Rapamycin 20.0 2 POLYSORBAT 80 (TWEEN 80) 150.0 3 Sorbitan monoleate 25.0 4 Neutral oil 75.0 5 Ascorbylpalmitate 0.5 6 Benzyl alcohol (DAB 10) 5.0

CLAIMS:

3. A pharmaceutical composition according to either claim 1 or claim 2 for the solubilisation of a sparingly soluble therapeutic agent selected from the group consisting of rapamycin, tacrolimus, deoxyspergualin, mycophenolate-mofetil, nifedipine, nimodipine, etoposide, and ibuprofen.

8. A pharmaceutical composition according to any one of claims 1-7, wherein component b) contains as pharmaceutically acceptable oil ground nut oil, sesame oil, sunflower oil, olive oil, corn oil, soybean oil, castor oil, cottonseed oil, rape-seed oil, thistle oil, grape-seed oil, fish oil or neutral oil, and component c) contains a nonionic surfactant with a hydrophilic component consisting of 15-60 units of ethylene oxid.